Evidence-to-Decision table

Problem Is the problem a priority?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	The ageing population means that the absolute numbers of those living with cognitive decline or dementia continue to rise, with an estimated prevalence of 75 million by 2030 and a new case of dementia diagnosed every three seconds (1). Anything that could reduce the incidence of cognitive decline or dementia would have huge importance for individual health, society and health care providers. A review carried out as part of the World Alzheimer Report (2014) reported that the presence of depression nearly doubled the risk of dementia (pooled effect size = 1.97, 95% CI 1.67 to 2.32). (2)	
Desirable Effects How substantial are the desirable anticipated effects?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	*Desirable effects* **Pharmacological interventions to treat depression (antidepressant medication) compared to usual care or placebo** No data on MCI or incident dementia. For cognitive function, the volume of evidence is high (12 RCTs, with 3 studies in vortioxetine, 4 studies in duloxetine, and single studies for sertraline, citalopram, escitalopram, phenelzine, nortriptyline) and overall quality of evidence is very low. A network meta-analyses (3) was conducted which found standardised mean difference in Digit Symbol Substitution Test (raw scores not provided). The review reported cognitive function was improved with vortioxetine (vs placebo) SMD 0.34 (0.18:0.49) and no effect for duloxetine SMD= -.13 (-0.03:0.28), sertraline SMD= -017 (-0.57:0.22), citalopram	A narrative review ((4)l) reported that the evidence supports a beneficial effect of Serotonin Norepinephrine Reuptake Inhibitors (SNRIs), Norepinephrine Reuptake Inhibitors (NRIs) or bupropion (a norepinephrine dopamine reuptake inhibitor) on cognition and suggest that Selective Serotonin Reuptake Inhibitors (SSRIs) would be especially useful in treating young patients. Mixed results were found with regards to psychological treatment for depression. One review (5) reported results in favour of huperzine A as a treatment for depression with positive cognitive outcomes, however the studies were considered to have a high risk of bias.

	SMD = -0.04 (-0.33:0.26), escitalopram SMD= -0.25 (-0.57:0.06), phenelzine SMD = -0.02 (-0.52:0.48), nortryptyline SMD = 0.01 (-0.56:0.58). Specifically, for the three studies of vortioxetine, which found significant improvement in cognitive function as measured on the DSST, the volume of evidence was low and the quality was moderate. There was no robust information on clinical significance. **Psychological interventions to treat depression compared to placebo or no intervention** No data available, inestimable.	

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	*Undesirable effects* **Pharmacological interventions to treat depression (antidepressant medication) compared to usual care or placebo** No data on undesirable outcomes were reported by the systematic reviews described above. **Psychological interventions to treat depression compared to placebo or no intervention** No data available, inestimable.	Undesirable effects of antidepressants in general include (6) 1. Selective Serotonin Reuptake Inhibitors (SSRIs; e.g. fluoxetine) Serious side-effects (these are rare): marked / prolonged akathisia (inner restlessness or inability to sit still); bleeding abnormalities in those who regularly use aspirin and other non-steroidal anti-inflammatory drugs. Common side-effects (most side-effects diminish after a few days; none are permanent): restlessness, nervousness, insomnia, anorexia and other gastrointestinal disturbances, headache, sexual dysfunction. Cautions: risk of inducing mania in people with bipolar disorder 2. Tricyclic antidepressants (TCAs; e.g. amitriptyline) Serious side-effects (these are rare): cardiac arrhythmia. Common side-effects (most side-effects diminish after a few days; none are permanent): orthostatic hypotension (fall risk), dry mouth, constipation, difficulty urinating, dizziness, blurred vision and sedation.

		Cautions: risk of switch to mania, especially in people with bipolar disorder; impaired ability to perform certain skilled tasks (e.g. driving) – take precautions until accustomed to medication; risk of self-harm (lethal in overdose); less effective and more severe sedation if given to regular alcohol users.

Certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**Pharmacological interventions to treat depression (antidepressant medication) compared to usual care or placebo** **Findings:** For cognitive function the certainty of the evidence is very low. No data on MCI, incident dementia, quality of life, adverse events, functional level or dropout rates. **Psychological interventions to treat depression compared to placebo or no intervention** **Findings:** No data available, inestimable.	

Values

Is there important uncertainty about or variability in how much people value the main outcomes?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Important uncertainty or variability ○ Possibly important uncertainty or variability	A review conducted by Anderson et al 2009(7) on public perceptions about cognitive health in the United States revealed that a large proportion of the population were concerned about	Additional sources like the Saga Survey (10) and Alzheimer's Research UK (11) have reported high percentage of people in the

○ Probably no important uncertainty or variability ● No important uncertainty or variability	declines in cognition or memory. Further studies in Australia (8) and the United Kingdom (9) (UK) and have shown a general trend of individuals being fearful of developing dementia. There is no evidence showing that individuals would oppose dementia risk reduction, of view cognitive decline favourably. Data from low and middle income countries is unavailable. There is no reason to believe there is important uncertainty about or variability in how much people value reducing the risk of cognitive decline and/or dementia.	UK fear dementia, even more so than cancer, and feel a prognosis would mean their life is over (62%)
Balance of effects Does the balance between desirable and undesirable effects favour the intervention or the comparison?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● Don't know	**Pharmacological interventions to treat depression (antidepressant medication) compared to usual care or placebo** No data on adverse effects was available e.g. drug-related side effects or interactions, so difficult to ascertain true balance of effects. May favour the use of vortioxetine to treat depression for reducing the risk of cognitive decline or dementia. Evidence does not favour other pharmacological interventions. **Psychological interventions to treat depression compared to placebo or no intervention** No data available, inestimable.	
Resources required How large are the resource requirements (costs)?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Large costs ● Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	Various medications can be used to treat moderate to severe depression and costs are dependent the drug administered (see additional considerations). No data on resources required were reported by the systematic reviews described above.	The WHO (12) recommendations for antidepressive medications are listed below. The prices are taken from the International Drug Price Indicator Guide (13) and are listed as price per unit. · Amitriptyline è Tablet: 25 mg; Median Price US$ (Supplier/Buyer) = 0.0072/0.0288; 75mg. (hydrochloride) (price not listed). · Fluoxetine è Solid oral dosage form: 20 mg (as hydrochloride); Median Price US$ (Supplier/Buyer) = not listed/0.0168 Depression treatment can be provided by non-specialists in primary care in LMIC (mhGAP)

Certainty of evidence of required resources

What is the certainty of the evidence of resource requirements (costs)?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ○ Low ○ Moderate ● High ○ No included studies	Antidepressive medication is commonly prescribed as a treatment option for moderate to severe depression. They are included in the WHO model list of essential medicines (12) and their costs are listed in the International Drug Price Indicator Guide (13).	The WHO Factsheet on Depression (http://www.who.int/en/news-room/fact-sheets/detail/depression) states that: "There are effective treatments for moderate and severe depression. Health-care providers may offer psychological treatments (such as behavioural activation, cognitive behavioural therapy [CBT], and interpersonal psychotherapy [IPT]) or antidepressant medication (such as selective serotonin reuptake inhibitors [SSRIs] and tricyclic antidepressants [TCAs]). Health-care providers should keep in mind the possible adverse effects associated with antidepressant medication, the ability to deliver either intervention (in terms of expertise, and/or treatment availability), and individual preferences. Different psychological treatment formats for consideration include individual and/or group face-to-face psychological treatments delivered by professionals and supervised lay therapists.

		Psychosocial treatments are also effective for mild depression. Antidepressants can be an effective form of treatment for moderate-severe depression but are not the first line of treatment for cases of mild depression. They should not be used for treating depression in children and are not the first line of treatment in adolescents, among whom they should be used with extra caution.”

Cost effectiveness

Does the cost-effectiveness of the intervention favour the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ○ Favours the intervention ○ Varies ● No included studies	Various medications can be used to treat moderate to severe depression and costs are dependent the drug administered, however there is evidence to show that antidepressives can be cost-effective in the treatment of depression (14) (see additional considerations). No data on cost effectiveness were reported by the systematic reviews described above.	The regional cost effectiveness of antidepressants in adults (retrieved from the Cost-Effectiveness Analysis in Disease Control Priorities, Third Edition (14): · Intervention = episodic treatment in primary care with older antidepressant drug (TCAs) à Cost per disability-adjusted life year averted or healthy life year gained, 2012 (US$) Sub-Saharan Africa = 1,410 Latin America and the Caribbean = 3,491 Middle East and North Africa = 3,171 Europe and Central Asia = 2,668 South Asia = 786

		East Asia and Pacific = 899 · Intervention = episodic treatment in primary care with newer antidepressant drug (SSRIs) à Cost per disability-adjusted life year averted or healthy life year gained, 2012 (US$) Sub-Saharan Africa = 1,395 Latin America and the Caribbean = 3,361 Middle East and North Africa = 3,057 Europe and Central Asia = 2,456 South Asia = 788 East Asia and Pacific = 894 Cost of combined medication and psychosocial interventions For depression, treatment in primary health care on an episodic basis costs between US$800 and US$3,500 per healthy life year gained; for a little more cost, as well as more overall health gain in the population, treatment on a proactive, maintenance basis is also a cost-effective alternative, because so many persons experience recurrent episodes (US$1,300–US$4,900 per healthy life year gained).
Equity What would be the impact on health equity?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Reduced ○ Probably reduced ○ Probably no impact ● Probably increased ○ Increased ○ Varies	A report from the Institute of Health on inequalities in cognitive impairment and dementia among older persons (15) studies health equities in England, they found that individuals with lower socioeconomic status (SES) were at increased risk of earlier onset of dementia, cognitive dysfunction at earlier stages of cognitive decline and impairment and tend to have fewer resources to cope with symptoms, as compared to higher SES groups. Further, lower SES groups are likely to live and age in environments that are physically and economically less	

○ Don't know	supportive of social connection physical activity or mental stimulation, which can increase the risk of cognitive impairment and dementia in later life. Based on this it is likely that interventions to reduce risk of cognitive decline and dementia will increase equity in health.	
Acceptability Is the intervention acceptable to key stakeholders?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ● Yes ○ Varies ○ Don't know	Varies; Drug-related side effects are a key consideration in acceptability of the intervention. There are no other apparent reasons for which pharmacological interventions for depression to reduce the risk of cognitive decline and/or dementia would not be acceptable to key stakeholders.	
Feasibility Is the intervention feasible to implement?		
JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ● Probably yes ○ Yes ○ Varies ○ Don't know	Yes, antidepressive medication already available and used in individuals with depression.	Diagnosis of depression may be challenging in some settings Continuous supply of antidepressants in primary care settings may be challenging in LMIC

References Summary

1. Prince, M. J.. World Alzheimer Report 2015: the global impact of dementia: an analysis of prevalence, incidence, cost and trends.. Alzheimer's Disease International; 2015.

2. Prince, M.,Albanese,E.,Guerchet,M.,& Prina,M.. World Alzheimer Report 2014: Dementia and risk reduction: An analysis of protective and modifiable risk factors. Alzheimer Disease International.; 2014.
3. Baune, B. T., Brignone, M., Larsen, K. G.. A Network Meta-Analysis Comparing Effects of Various Antidepressant Classes on the Digit Symbol Substitution Test (DSST) as a Measure of Cognitive Dysfunction in Patients with Major Depressive Disorder. Int J Neuropsychopharmacol; Feb 1 2018.
4. Salagre, E., Sole, B., Tomioka, Y., Fernandes, B., Hidalgo-Mazzei, D., Garriga, M., Jimenez, E., Sanchez-Moreno, J., Vieta, E., Grande, I.. Treatment of neurocognitive symptoms in unipolar depression: A systematic review and future perspectives. Journal of Affective Disorders; Oct 2017.
5. Zheng, Wei, Xiang, Ying-Qiang, Ungvari, Gabor S., Chiu, Helen F., Ng, Chee H., Wang, Ying, Xiang, Yu-Tao. Huperzine A for treatment of cognitive impairment in major depressive disorder: A systematic review of randomized controlled trials. Shanghai Archives of Psychiatry; Apr 2016.
6. World,Health Organisation,. WHO Mental Health Gap Action Programme (mhGAP) Intervention Guide for mental, neurological and substance use disorders in non-specialized health settings. Retrieved from: http://www.who.int/mental_health/mhgap/evidence/en/;
7. Anderson, L. A.,Day,K. L.,Beard,R. L.,Reed,P. S.,& Wu,B.. The public's perceptions about cognitive health and Alzheimer's disease among the US population: a national review. The Gerontologist; 2009.
8. Low, L. F.,& Anstey,K. J.. Dementia literacy: recognition and beliefs on dementia of the Australian public.. Alzheimer's & dementia: the journal of the Alzheimer's Association; 2009.
9. Yeo, L. J.,Horan,M. A.,Jones,M.,& Pendleton,N.. Perceptions of risk and prevention of dementia in the healthy elderly. Dementia and Geriatric Cognitive Disorders; 2007.
10. Healthcare., Saga. Dementia more feared than Cancer new Saga Survey reveals.. Retrieved from https://www.dementiastatistics.org/statistics-about-dementia/public-perception/; 2016.
11. Society., Alzheimer's. Dementia Awareness Week.. Retrieved from https://www.saga.co.uk/newsroom/press-releases/2016/may/older-people-fear-dementia-more-than-cancer-new-saga-survey-reveals.aspx; 2016.
12. World,Health Organization.,. WHO model list of essential medicines: 20th list, March 2017. 2017.
13. , . Management Sciences for Health . International Drug Price Indicator Guide.. Retrieved from: http://mshpriceguide.org/en/home/; 2014.
14. Horton, S.. Cost-Effectiveness Analysis in Disease Control Priorities, Third Edition.. Retrieved from http://dcp-3.org/sites/default/files/chapters/DCP3%20Mental%20Health%20Ch_12.pdf ,; 2018.
15. Daly., S. & Allen.,J.. Inequalities in mental health cognitive impairment and Dementia among older people. London, Institute of Health Equity.. Retrieved from http://www.instituteofhealthequity.org/resources-reports/inequalities-in-mental-health-cognitive-impairment-and-dementia-among-older-people; 2016.